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A Systematic Review of Interleukin (IL) -1β in Post-Traumatic Stress Disorder: Evidence from Human and Animal Studies

(Short Title: Systematic review of IL-1β and PTSD)

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Abstract

Pro-inflammatory cytokines, such as IL-1β, have been implicated as underlying pathophysiological mechanisms and potential biomarkers of Post-Traumatic Stress Disorder (PTSD). This systematic review examines data regarding IL-1β production/concentration in human and animal studies of PTSD. In accordance with PRISMA guidelines, relevant articles from PubMed were reviewed from inception until 10th July 2017.

Nineteen studies were eligible for inclusion. Animal studies demonstrated increased hippocampal IL-1β in rodent models of PTSD. Several immunomodulatory drugs were shown to reduce elevated IL-1β levels and anxiety-like behaviours in animals. Human cross-sectional studies showed contradictory results; serum and plasma IL-1β concentrations in PTSD patients were either elevated or did not differ from control groups. *In-vitro* IL-1β production by stimulated cells demonstrated no difference between PTSD and control participants, although spontaneous i*n-vitro* production of IL-1β was increased in the PTSD group. The findings from two longitudinal studies were inconsistent.

Given the conflicting findings, it is premature to consider IL-1β as a biomarker of PTSD. Anti-inflammatory agents may reduce IL-1β, and be a potential basis for future therapeutic agents in PTSD treatment. More longitudinal research is needed to better understand the role of IL-1β in the development and/or maintenance of PTSD.

Introduction

Post-traumatic Stress Disorder (PTSD) is a chronic psychiatric disorder that can develop in response to exposure to a catastrophic threat. Triggers can include war, sexual or physical assault, and natural disasters. Throughout history the condition has had various labels, including 'Shell Shock' and 'Stress Response Syndrome', although it was not until the late twentieth century that it was included in the diagnostic classifications used in psychiatry practice today (American Psychiatric Association 2013). PTSD was first included in the Diagnostic and Statistical Manual (DSM) of the American Psychiatric

Association in 1980, followed by inclusion in the World Health Organisation's International Classification of Diseases (ICD) over a decade later, in 1992 (World Health Organization 1992). Although similar, the two systems provide differing criteria for which to diagnose patients potentially suffering from PTSD.

PTSD diagnosis and assessment

PTSD diagnosis. Specifically, the ICD-10 classification requires patients to have been exposed to a stressful event which is perceived as threatening and causes them distress (World Health Organization 1992). No minimum length of exposure is stated, however, symptoms should begin within six months of the traumatic exposure. The trauma is regularly revisited by the patient through intrusive dreams, memories, or flashbacks, particularly if the individual finds themselves in a similar situation to the initial trauma. Patients actively avoid situations associated with the trauma or block out memories pertaining to the event. In addition, patients should experience two or more of the following symptoms in order for the diagnosis to be made: difficulty falling asleep, lability of mood or emotional outbursts, concentration deficits, hyper-arousal or an increased startle response. These symptoms ought to be of new onset following the trauma, and are indicative of amplified psychological sensitivity (World Health Organization 1992).

Similarly, to fulfil a diagnosis of PTSD according to DSM-5 criteria (American Psychiatric Association 2013), patients should have experienced an event involving actual or threat of death, sexual or physical violence, or serious injury. This may be through direct exposure, witnessing an event, or being informed that an acquaintance or relative was involved in a traumatic event. Akin to the ICD-10 classification, re-experiencing the trauma is required, although not necessarily as nightmares or flashbacks. Severe emotional distress or physical reactivity can also be diagnostic. Avoidance of circumstances or thoughts related to the trauma and two or more negative emotions must also be present, or become progressively worse following the trauma. These may include feelings of isolation, persecutory thoughts, or being unable to remember facts relating to the event. The patient also needs

to suffer from 2 or more symptoms of hyper-arousal, again equivalent to ICD-10 criteria. Unique to DSM-5, the patient's symptoms must be severe enough to cause distress and deterioration of normal function, which cannot be explained by other factors, such as changes in medication or co-morbid pathology, and should persist for a minimum of one month following the initial trauma. All elements of the criteria must be fulfilled for over 1 month duration for a confident diagnosis to be made (American Psychiatric Association 2013).

Assessment of PTSD. The ICD-10 or DSM-5 criteria are commonly used for research purposes and for the clinical diagnosis of PTSD. In clinical as well as in research practice, the structured clinical interview for the DSM-IV axis I disorders (SCID-IV), and more recently the SCID-5, are standard validated diagnostic tools with good sensitivity and inter-rater reliability that are used to make the diagnosis according to DSM-IV and DSM-5 (Elhai et al 2008; Lobbestael et al 2011). In research, self-administered PTSD questionnaires are also used, including the PTSD Checklist (PCL; Blanchard et al 1996; a civilian and military version are also available, PCL-C and PCL-M respectively; Weathers et al 2013), the Los Angeles Symptom Checklist (LASC; King et al 1995), and the Posttraumatic Diagnostic Scale (PDS; Foa et al 1997; Sheeran and Zimmerman 2002). Although quicker to perform, these measures may have a tendency to over-diagnose patients (Griffin et al 2004). Currently, the gold standard tool for assessing PTSD symptom severity is the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5; American Psychiatric Association 2013; Blake et al 1995).

Animal models of PTSD. Rodents are typically used and are subjected to various validated stress-paradigms in order to simulate a PTSD-like state in the animals (Goswami et al 2013). Two examples are the Stress-Enhanced Fear Learning (SEFL) model and the Single Prolonged Stress (SPS) procedure. In SEFL rodents are given multiple electric shocks, at a later time they are then placed in a different environment and given a single shock as a reminder of the original stressful event. Freezing time and/or immobility is used as a measure of a learned fear response (Rau et al 2005). In the SPS procedure, several stressors are administered to the rodent, including restraint, forced swimming, and

ether, followed by a period of inactivity (Yamamoto et al 2009). In PTSD models, various behavioural tests, including the open field test, are then subsequently performed to confirm the presence of pre-defined PTSD traits, such as hyperarousal and social withdrawal. Following the implementation of an animal model, medication trials, behavioural experiments, and cellular analysis can then be performed.

The pathophysiology of PTSD

An important biological factor involved in the pathophysiology of PTSD seems to be brain morphology and function. Studies have demonstrated gross morphological differences between the brains of PTSD patients and healthy controls (Woon and Hedges 2009; Zandieh et al 2016). These include changes to the hippocampus, amygdala, and prefrontal cortex, which may account for the symptoms of PTSD, given their involvement in memory, emotion and personality, and behavioural functioning. Specifically, hippocampal volume and grey matter density were found to be reduced in PTSD patients compared to healthy controls (Gilbertson et al 2002). Also, studies have demonstrated reduced amygdala volumes in PTSD patients (Morey et al 2012). Interestingly, stress has been shown to lead to increases in pro-inflammatory cytokines (Lopez-Castejon and Brough 2011; Wilson et al 2013) and kynurenine pathway metabolites which can both be neurotoxic in the hippocampus, the amygdala and prefrontal cortex (Kim and Won 2017).

Current review

As PTSD is a heterogeneous disorder, it is likely that there are multiple mechanisms underlying the development and maintenance of the disorder and therefore, several possible biomarkers. Inflammatory processes are one possible biomarker of PTSD (Michopoulos et al 2015). Existing literature indicates that pro-inflammatory cytokines could be a contributing factor to the pathophysiology of PTSD and play a role in PTSD-related elevated risk for cardiovascular, autoimmune, and neurodegenerative diseases, although the precise mechanisms remain unclear.

The current review will focus upon IL-1β as it is a key cytokine that has been implicated in neuroplasticity and the process of memory formation (Lopez-Castejon and Brough 2011). Secreted from macrophages, microglia and astrocytes, IL-1β has roles in host defence, tissue injury during acute and chronic inflammatory disease, and auto-inflammatory conditions. A recent meta-analysis found that several pro-inflammatory cytokines, including IL-1β, are elevated in PTSD patients in comparison to control groups (Passos et al 2015). This meta-analysis focused on human cross-sectional *in-vivo* measurements and did not account for *in-vitro* measurements, longitudinal investigations, nor animal studies. Thus, the current review is warranted to provide a more comprehensive and up-to-date summary of the available literature. The purpose of this systematic review is to summarise the evidence regarding IL-1β and PTSD in human and animal literature, with a view to adding to current understanding of the condition and its pathophysiology, and to assess its potential as a biomarker for PTSD and its treatment. If an association is identified between IL-1β and PTSD, this could provide a potential future treatment target for PTSD, as blocking medications are available.

Methods

Selection Criteria

Articles were eligible for inclusion in the review if they reported on original research pertaining to both IL-1β and PTSD in human or animal studies. Specifically, studies of any design that assessed IL-1β production *in-vitro* or IL-1β concentration in the serum, plasma, or cerebrospinal fluid (*in-vivo*) of individuals with PTSD were eligible for inclusion. Studies were included if they reported a group and/or longitudinal comparison of IL-1β concentration and/or production. Publications reporting on the measurement of IL-1β in animal models of PTSD were also included.

Studies were excluded if: (i) they did not report group or longitudinal comparisons in concentration or production of IL-1β; (ii) they presented purely genetic or IL-1β receptor data; (iii) participants were not formally diagnosed with PTSD according to a validated assessment tool or diagnostic criteria; and (v) life trauma, childhood trauma or distress caused by chronic illness, rather than PTSD, was

investigated. Review articles, meta-analyses, conference proceedings/abstracts, editorials, letters, book chapters, and unpublished theses were also not included.

Search Strategy

Using PubMed and in accordance with the PRISMA guidelines (Moher et al 2009), a search from inception until 10th July 2017 was conducted. The following search terms were used to identify all potentially eligible records:

((("post-traumatic stress disorder"[Title/Abstract]) OR ("PTSD"[Title/Abstract]) OR ("posttraumatic stress disorder"[Title/Abstract]) OR ("post traumatic stress disorder"[Title/Abstract])) AND (("interleukin-1"[Title/Abstract]) OR ("interleukin-1β"[Title/Abstract]) ("interleukin-1 β"[Title/Abstract]) OR ("interleukin-1 beta"[Title/Abstract]) OR ("interleukin-1beta"[Title/Abstract]) OR ("interleukin 1"[Title/Abstract]) OR ("interleukin 1β"[Title/Abstract]) OR ("interleukin 1 β"[Title/Abstract]) OR ("interleukin 1 beta"[Title/Abstract]) OR ("interleukin 1beta"[Title/Abstract]) OR ("IL-1"[Title/Abstract]) OR ("IL-1β"[Title/Abstract]) OR ("IL-1 β"[Title/Abstract]) OR ("IL-1 beta"[Title/Abstract]) OR ("IL-1beta"[Title/Abstract]) OR ("IL 1"[Title/Abstract]) OR ("IL 1β"[Title/Abstract]) OR ("IL 1 β"[Title/Abstract]) OR ("IL 1 beta"[Title/Abstract]) OR ("IL 1beta"[Title/Abstract]))

This search was supplemented by internet searches and hand-searches of reference lists of included papers and potentially relevant reviews. Citation tracking in Web of Science was also performed. The abstracts of identified articles were subsequently screened for eligibility according to pre-set inclusion and exclusion criteria, as described above. Potentially eligible records were further reviewed in full text. Subsequently, the articles included in the qualitative synthesis were categorized into animal and human studies and then further divided according to their study design. An overview of the literature search is shown in Figure 1.

Data Extraction

The data from all eligible studies was extracted into an electronic summary table by the first author (AW), which was then checked by another author (BD). Information collected related to the sample characteristics, method of PTSD assessment and measurement of IL-1β, and relevant findings.

INSERT FIGURE I HERE

Results

Characteristics of included studies

A total of 19 articles were eligible for inclusion in this review. Eight of the included articles used animal models of PTSD to investigate the relationship between IL-1β and PTSD (Aga-Mizrachi et al 2014; Deslauriers et al 2017; Jones et al 2015; Lazuko et al 2017; Lee et al 2016; Liu et al 2016; Peng et al 2013; Zimmerman et al 2012). Twelve studies assessed IL-1β concentration or production in humans. Nine of these were *in-vivo* cross-sectional human studies measuring plasma, or serum concentration of IL-1β (Bersani et al 2016; Hoge et al 2009; Jergović et al 2015; Lindqvist et al 2014; Oganesyan et al 2009; Spivak et al 1997; Tucker et al 2004; von Känel et al 2007; Zhou et al 2014). Of these, two studies also assessed serum IL-1β longitudinally in individuals with PTSD (Jergović et al 2015; Tucker et al 2004) and one study reported both human and animal data (Zimmerman et al 2012). Two additional human cross-sectional study assessed IL-1β production *in-vitro* (Gill et al 2008; Gola et al 2013).

Study findings: Animal studies

All included animals studies used rodents in their animal models of PTSD. A variety of animal models were used (e.g. SPS, SEFL, enhanced SPS, predator scent exposure) to induce PTSD-like traits; the majority involved applying a shock to the foot of the animal. Most studies measured hippocampal IL-1β levels (Jones et al 2015; Lee et al 2016; Liu et al 2016; Peng et al 2013), with three remaining studies measuring serum concentrations of IL-1β (Aga-Mizrachi et al 2014; Lazuko et al 2017; Zimmerman et al 2012) and the other measuring brain protein levels (Deslauriers et al 2017). The results of these studies are presented in Table I.

Elevated serum IL-1β levels in the PTSD-groups, as compared to the control groups were identified (Aga-Mizrachi et al 2014; Lazuko et al 2017). In Aga-Mizrachi et al (2014), these elevated serum IL-1β levels were subsequently reduced upon administration of antidepressants (desipramine and fluoxetine) or methylphenidate, a stimulant of the central nervous system. The combination of the SSRI fluoxetine and methylphenidate reduced IL-1β to undetectable levels. In contrast, Zimmerman et al (2012) reported that IL-1β serum levels did not differ between the stressed and non-stressed groups. However, when stressed mice were administered mEN101, an oligonucleotide with anxiolytic effects, levels of IL-1β were significantly lower than in the non-treated stress group. Three studies also reported increased IL-1β levels in the hippocampus of stress-induced rats (Jones et al 2015; Lee et al 2016; Peng et al 2013). Specifically, Jones et al (2015) showed that hippocampal IL-1β immunoreactivity and mRNA expression increased in a time-dependent manner post-stressor. This effect was most prominently observed in the dentate gyrus of the dorsal hippocampus. Furthermore, stress-induced rats given morphine 48-hours post-stressor, showed a significant reduction in hippocampal IL-1β levels. Similarly, in Peng et al., the hippocampal IL-1β levels reduced in a dose-dependent manner with the administration of gastrodin, a main constituent of a Chinese herbal medicine. These reductions in IL-1β levels were also associated with improvements in PTSD-like behaviour. Additionally, Lee et al (2016) found that the elevated levels of IL-1β hippocampal mRNA expression observed in the stressed rats, was reduced by the administration of fluoxetine to similar IL-1β levels seen in the non-stressed rats. In contrast, Liu et al (2016) found no significant difference in hippocampal IL-1β levels between SPS-exposed rats and controls; however, elevated levels of malondialdehyde, a marker of oxidative stress, were found in the hippocampus (Yang et al 2013). Deslauriers et al (2017) also found no difference in IL-1β levels in predator stress exposed male C57BL/6 mice compared to non-exposed mice.

INSERT TABLE I HERE

Study findings: Human Studies

PTSD assessment. In the majority of studies, PTSD diagnosis had been made using versions of the DSM or ICD. The majority of studies also used validated questionnaires to measure PTSD symptom severity in the study. The CAPS was used in 8 studies, 2 of these used it in combination with the SCID (Bersani et al 2016; Tucker et al 2004) and one with the PCL-M (Zhou et al 2014). One study (Hoge et al 2009) used the Short Post-Traumatic Stress Disorder Rating (SPRINT; Connor and Davidson 2001) , one used the LASC (Jergović et al 2015) and one the Hebrew version of the PTSD Inventory (Spivak et al 1997).

Cross-sectional studies measuring IL-1β in-vivo. Five of the included cross-sectional studies identified elevated IL-1β concentrations in the plasma or serum of PTSD participants, as compared to a control group (Hoge et al 2009; Oganesyan et al 2009; Spivak et al 1997; Tucker et al 2004; Zimmerman et al 2012). The remaining five studies found no difference in serum or plasma concentrations of IL-1β between participants with and without PTSD (Bersani et al 2016; Jergović et al 2015; Lindqvist et al 2014; von Känel et al 2007; Zhou et al 2014). Details of these studies are presented in Table II.

Of note, plasma IL-1β concentration were found to positively correlate with recognised PTSD symptoms, including re-experiencing, avoidance and co-morbid anxiety and depression, although when controlling for co-variates, such as depression, the results became insignificant (von Känel et al 2007). Spivak et al (1997) reported a positive correlation between serum IL-1β concentration and PTSD symptom duration. This association remained even when adjusting for subject demographics. Additionally, Oganesyan et al (2009) noted a positive correlation between IL-1β and CH50 levels, a ~~marker~~ measure of activation of the classic complement pathway, suggestive of an immunological component to PTSD pathophysiology. Zimmerman et al (2012) identified a significant inverse correlation between IL-1β serum levels and hippocampal volume in a subset of PTSD patients (n=5). No correlations were identified between IL-1β serum levels and other brain structures.

Cross-sectional studies measuring IL-1β in-vitro. Two studies assessed IL-1β production using *in-vitro* methods; details regarding these are presented in Table II. Gola et al (2013) assessed spontaneous and lipopolysaccharide (LPS)-induced IL-1β production in peripheral blood mononuclear cells (PBMCs)

of refugees, with and without PTSD. Participants with PTSD were found to spontaneously produce elevated levels of IL-1β, as compared to those without PTSD. Spontaneous IL-1β production and PTSD symptom severity (in PTSD group only) were found to be correlated at trend level. However, no difference in LPS-induced IL-1β production was observed between these groups. Similarly, Gill et al (2008) found no differences between females with PTSD, females who experienced trauma but did not go on to develop PTSD, and healthy females in stimulated phytohaemagglutinin (PHA) combined with LPS production of IL-1β from whole blood samples.

Longitudinal studies measuring IL-1β in-vivo. Two of the included studies employed a longitudinal design (Jergović et al 2015; Tucker et al 2004). The results of these studies are presented in Table II. In Jergović et al (2015), serum IL-1β was measured on two separate occasions, three months apart, in male Croatian combat veterans with PTSD. An increase in IL-1β concentration was found between the first and second assessment. Of note, IL-1β was not detectable in a proportion of participants at both time points. Tucker et al (2004) performed a double-blind randomised controlled trial of selective serotonin reuptake inhibitors (sertraline and citalopram) and placebo treatment in outpatients with PTSD. In contrast to Jergović et al (2015), serum IL-1β was found to significantly decrease over the trial for all treatment groups.

INSERT TABLE II HERE

Discussion

The current review summarises and integrates the existing data on concentrations and production of IL-1β in PTSD. Data from the included animal studies demonstrated an increase in serum IL-1β concentration and a time-dependent elevation in hippocampal IL-1β levels in PTSD-modelled rats (Aga-Mizrachi et al 2014; Jones et al 2015; Lazuko et al 2017; Lee et al 2016; Peng et al 2013). In particular, this was observed in the dentate gyrus of the dorsal hippocampus, suggesting that inflammation in this neural region, with roles in memory processing and autonomic functions, may be integral to PTSD pathophysiology. Conversely, no difference in IL-1β levels between PTSD-modelled

rats and controls was observed in three studies (Deslauriers et al 2017; Liu et al 2016; Zimmerman et al 2012), highlighting the need for further research into cytokine levels in animal models of PTSD. As a centre for emotional processing, dysregulation of inflammatory processes in the amygdala may equally contribute to PTSD symptoms, particularly those effecting mood (Shin et al 2006). However, Jones et al. identified no increase in IL-1β in the basolateral amygdala. More research is needed to assess IL-1β levels in alternative neural regions that have been implicated in PTSD.

Interestingly, in the animal studies a range of treatment medications were found to reduce both IL-1β levels and PTSD-like behaviours, including antidepressants (Aga-Mizrachi et al 2014), apocynin, an inhibitor of NADPH oxidase (Liu et al 2016), and gastrodin, an inhibitor of nitric oxide synthase (Peng et al 2013). This not only contributes further evidence to the role of oxidative stress and inflammatory mechanisms in PTSD pathophysiology, but also suggests that such compounds may be useful as future pharmacological therapies for PTSD. Similarly, morphine was found to decrease IL-1β in the dorsal hippocampus (Jones et al 2015), suggestive of a protective role of opioid signalling in the physiological response to trauma. In summary, the majority of animal studies suggest an associative link between elevated IL-1β and PTSD; however, the small number of animal studies identified in this review makes drawing solid conclusions difficult, particularly concerning serum IL-1β, where only three studies were available.

Half of the human cross-sectional studies found that serum or plasma IL-1β concentrations were elevated in those with PTSD compared to control participants (Hoge et al 2009; Oganesyan et al 2009; Spivak et al 1997; Tucker et al 2004; Zimmerman et al 2012). Spontaneous production of IL-1β was also found to be elevated in PTSD compared to non-PTSD groups (Gola et al 2013). The remaining studies found no significant difference in serum or plasma IL-1β concentrations between PTSD patients and controls (Bersani et al 2016; Lindqvist et al 2014; von Känel et al 2007; Zhou et al 2014) (Jergović et al 2015). Stimulated production of IL-1β also did not differ between PTSD and control groups (Gill et al 2008; Gola et al 2013). One factor that may contribute to the variable outcomes

observed is participant's use of corticosteroid treatments (e.g. prednisone, prednisolone and dexamethasone). These medications have anti-inflammatory effects (Greaves 1976), however, long-term steroid treatment was an exclusion criteria in only one study (Zhou et al 2014). Given the mixed findings and the lack of control for potential confounders such as glucocorticoid treatment, it would be premature to consider IL-1β as a biomarker of PTSD. Moreover, given that other pro-inflammatory cytokines (e.g. Il-6 and TNF-α) were also shown to be elevated in patients with PTSD, as compared to controls, a combined pro-inflammatory cytokine score/index may be most appropriate as a biomarker. In addition, levels of these cytokines, and others, are typically elevated in people with moderate to severe depression (Dahl et al 2014). Therefore, cytokine levels may be a general marker of psychopathology, rather than specifically for PTSD.

There is much evidence from animal studies showing that both chronic and acute stress paradigms result in elevated levels of pro-inflammatory cytokines (e.g. Cosen-Binker et al 2004; Liu et al 2012). This includes elevated protein and mRNA levels of IL-1β in the brain (e.g. Minami et al 1991; Nguyen et al 1998; Pugh et al 1999). Furthermore, in humans, acute psychological stress has been shown to increase IL-1β gene expression (Brydon et al 2005). The mechanisms as to how stress leads to an increase of pro-inflammatory cytokine production is still unclear. Pro-inflammatory cytokines, including IL-1β, have an effect on the brain, and therefore, behaviour, via several mechanisms (Quan 2008). For example, they have been shown to have effects on neurotransmitter synthesis, release and reuptake; neuroendocrine activity; neural plasticity; and changes in brain circuitry (Capuron and Miller 2011). Therefore, stress may results in an increased production of pro-inflammatory cytokines and consequently trigger neurobiological changes, which may contribute to the development and/or maintenance of psychiatric disorders, such as PTSD and depression.

As previously mentioned, the hippocampus is a key brain structure implicated in PTSD (e.g. Kitayama et al 2005; O'Doherty et al 2015). In the animal studies described above, elevated IL-1β was observed in the hippocampi of PTSD-modelled rats and in one of the included human studies, IL-1β serum levels

were found to be inversely correlated with hippocampal volume in PTSD patients (Zimmerman et al 2012) which may imply that elevated IL-1β production possibly leads to a decrease in hippocampal volume. Moreover, it has been suggested that elevated IL-1β concentration in the hippocampus may impair synaptic plasticity and memory (Patterson, 2015). However, the mechanisms as to how IL-1β influences hippocampal volume and synaptic plasticity are not clear.

Only two longitudinal studies of IL-1β levels in PTSD patients were identified in this review, reporting contradictory findings in terms of IL-1β, however, both finding improvements in PTSD symptoms (Jergović et al 2015; Tucker et al 2004). Specifically, in a randomised controlled trial of anti-depressant medications (placebo vs. sertraline vs. citalopram), all treatment groups showed decreases in serum IL-1β at the end of treatment, compared to baseline (Tucker et al 2004). In contrast, Jergović et al (2015) found that serum concentrations of IL-1β increased over a period of 3-months. However, in approximately half of the samples IL-1β could not be detected, and this therefore limits our ability to draw firm conclusions. As there is limited longitudinal data on IL-1β concentrations in PTSD, future research should measure IL-1β over the treatment course to better determine how IL-1β is related to changes in PTSD symptom severity and associated treatment response. Given not everyone who is exposed to a traumatic event will go on to develop PTSD, prospective studies would also be of benefit in elucidating the role of cytokines in the development and maintenance of PTSD (Keane et al. 2009).

Methodological considerations of the included studies. Many of the included studies did not covary for potential confounding variables in their analyses or study design that could affect the cytokine concentration, for example, BMI, smoking, medication (e.g. corticosteroid treatments), blood sugar level and total cholesterol. High co-morbid rates of dyslipidaemia, coronary heart disease, smoking and obesity amongst PTSD sufferers have been observed. Given that factors associated with these (e.g. BMI, physical illnesses, medication, smoking; Dugué et al 1996) have been shown to impact upon cytokine concentrations, it would be important for future studies to take factors such as these into consideration. Another factor to take into consideration is that the studies included in the current

review used different PTSD assessment/diagnostic tools. The measures used to assess PTSD symptoms vary considerably on a range of factors, including number of items, response format, time frame, and degree of detailed enquiry. Therefore, studies may not be directly comparable with regards to PTSD symptom severity.

There are also several limitations of the included studies based on factors related to the sample that limit the generalisability of the findings. Generally, sample sizes are small and the majority of study's samples consisted of exclusively or predominantly males. This may be attributable to the inclination to study combat-associated PTSD, with males being more highly represented in armed services. However, considering the increased incidence of PTSD in females (Carmassi et al 2014), the presented data may not be able to account for potential sex differences in IL-1β levels and may not be generalisable to females with PTSD. Furthermore, many samples are limited to veterans with trauma exposure due to combat. We cannot be sure that individuals with different experiences of trauma exposure (e.g. with regards to time, type and extent of trauma exposure) will demonstrate similar alterations in cytokine levels (Wang and Young 2016). Future studies should consider investigating cytokine levels in non-military PTSD patients. Finally, several of the included studies used trauma controls, i.e. people that had previously been exposed to trauma (e.g. combat) but did not go on to develop PTSD, which may account for the findings observed in some of the studies. Although not meeting the clinical threshold for a formal PTSD diagnosis, the experience of trauma may cause intrinsic changes in cellular processes, which may result in a heightened pro-inflammatory status in the control group participants. For example, MRI studies have since shown cingulate isthmus and prefrontal volume reduction, not only in PTSD individuals, but also in those without diagnosed PTSD who have been previously exposed to traumatic events (Eckart et al 2011). However, it is still unclear as to what extent trauma exposure can influence inflammatory markers, even without the development of PTSD (Passos et al 2015).

Limitations of the current review. Our systematic review has a number of limitations. Firstly, PubMed was the only source of articles searched, potentially excluding some of the published literature on the subject. However, a hand-search was also conducted to identify any that may have been missed through the initial search. Secondly, given that several other pro- and anti-inflammatory cytokines have been implicated in PTSD, the exclusive focus on IL-1β may be deemed too narrow. Thirdly, as several of studies in this review, both animal and human, reported elevated IL-1β in PTSD groups, publication bias must also be taken into account.

Conclusion

Animal studies suggest that IL-1β expression/production, particularly in the hippocampus, may be involved in the underlying pathophysiology of PTSD. Anti-inflammatory agents were shown to reduce elevated IL-1β levels in animal studies, and therefore may be a potential basis for future therapeutic agents in PTSD treatment. The conflicting findings from human studies suggest that it is premature to consider IL-1β as a biomarker of PTSD. However, these findings need to be considered in light of a range of methodological issues, such as confounding variables and sample characteristics. Therefore, more research, taking into account these issues, is needed to determine whether IL-1β can be considered a specific biomarker of, ~~PTSD~~ and therefore a potential therapeutic target for PTSD. Longitudinal research is needed to better understand the role of IL-1β in the development and/or maintenance of PTSD.

Author Disclosure Statement

No competing financial interests exist.

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